

May 14, 2004

Thomas M. Gray, M.S., D.A.B.T.
Senior Toxicologist
The American Petroleum Institute
Petroleum HPV Testing Group
1220 L. Street, N.W.
Washington, DC 20005-4070

Dear Dr. Gray:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Gas Oils Category posted on the ChemRTK HPV Challenge Program Web site on December 16, 2003. I commend The American Petroleum Institute, Petroleum HPV Testing Group for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the HPV Testing Group advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission: Gas Oils Category

Summary of EPA Comments

The sponsor, The American Petroleum Institute, submitted a test plan and robust summaries to EPA for the Gas Oils category dated November 7, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 16, 2003. The category is described by 28 CAS Nos. that define mixtures of paraffinic, olefinic, naphthenic, and aromatic hydrocarbons, and mixed aromatic cycloalkanes with carbon numbers ranging from C₉ to C₃₀. The names and CAS registration numbers for each of these substances are given below under Category Definition.

EPA has reviewed this submission and has reached the following conclusions:

1. General. Because of the complexity of these substances as well as the lack of information on several of the components of the substances, the test plan was difficult to evaluate as submitted. EPA is requesting additional information before a full evaluation of the test proposal can be made.
2. Category Definition. The percentages of the heteroatom-containing compounds and 3- to 7-ring PACs need to be more completely defined for the substances in this category. In addition, the submitter needs to supply more information on the chemical structures and percentages of the additives used in the distillate fuels.
3. Category Justification. Pending additional information on some of the components of the category members and the likely toxicity of these components, EPA agrees that the category is reasonable. Although none of the members will be compositionally consistent over time, the substances are composed of predominantly saturated or aromatic hydrocarbons and are bounded by a given boiling point range. Given the complexity of the category, as well as the variation in mixture components, the subdivisions within the category (distillate fuels, predominantly aromatic gas oils, and predominantly saturated gas oils) appear appropriate.
4. Physicochemical Properties. The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.
5. Environmental Fate. For biodegradation, EPA agrees conditionally that two gas oil streams be tested. However, the submitter needs to characterize the two gas oil streams in order to identify their main components. The submitter needs to provide fugacity data using a level III model.
6. Health Effects. EPA agrees that additional testing is needed for the reproductive toxicity endpoint using a reproductive/developmental screening test for the distillate fuels. However, because of limitations in the available repeated-dose studies for the predominantly aromatic compounds, EPA recommends that the submitter expand the proposed reproductive/developmental screening test for this subgroup of chemicals by including a repeated-dose component. EPA reserves judgment on whether to conduct reproductive toxicity testing for the predominantly saturated gas oils pending a full study report of the 13-week dermal study from the submitter so that the reproductive effects can be independently evaluated.

Data supplied for the chromosomal aberrations endpoint for the predominantly aromatic gas oils are adequate. Although adequate data may exist to satisfy the mutagenicity endpoint for predominantly aromatic gas oils as well as the genotoxicity endpoints for the other subcategories, additional details need to be provided in the robust summaries so that the study adequacy can be independently assessed.

The exact nature of any testing in addition to the above data and tests, however, depends on the additional information that is supplied on the percentages of components that have not been well characterized (see Category Definition above) in the category mixtures and their associated toxicities.

The submitter should consider testing substances with a range of each of the components likely to demonstrate appreciable toxicity for one or more SIDS endpoints.

7. Ecological Effects. EPA agrees that testing two gas oil streams (one with predominantly aromatic hydrocarbons and one with predominantly saturated hydrocarbons) for acute toxicity is appropriate for any substances that are likely to have a log K_{ow} less than 4.2. In addition, EPA believes that chronic toxicity testing is also necessary for each of these gas oil subcategories to meet data adequacy for environmental toxicity concerns. Although the submitter is not proposing additional testing of the distillate fuels, the additives content needs to be characterized for these fuels before EPA can determine whether the existing data are adequate for this subcategory.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA Comments on the Gas Oils Category Challenge Submission

Category Definition

The gas oils category contains distillate fuels (including diesel fuels and fuel oils) and the refinery streams (gas oil streams) used in the production of these fuels. The submitter stated that the members of the gas oils category are covered under 28 CAS registry numbers. The distillate fuels are blended from gas oil streams, which are those stocks obtained from the atmospheric distillation of crude oil (straight-run) and from the secondary processing of residuum remaining after atmospheric or vacuum distillation of crude oil. These substances contain linear and branched paraffins, naphthenes, olefins, aromatic hydrocarbons, and mixed aromatic cycloalkanes ranging in carbon number from C_9 to C_{30} . The composition of saturates is 18-86% and the composition of aromatics is 14-82% in distillate fuels and refinery streams. Refinery streams obtained from secondary processing steps typically contain higher portions of aromatic and olefinic hydrocarbons. In addition to substituted benzenes, these aromatics also can include polycyclic aromatic compounds (PACs). Straight-run gas oils contain mainly 2- and 3-ring PACs with lower levels of 4- to 6-ring PACs. Gas oils containing heavier atmospheric or vacuum distillate, or cracked gas oil components, are likely to contain higher amounts of 4- to 6-ring PACs. The blended distillate fuels, in addition to containing the hydrocarbons from their blending stocks, may also contain performance additives such as flow improvers, corrosion inhibitors, defoamers, dyes/markers, anti-oxidants, stability improvers, cetane improvers, detergents, and anti-static additives. The submitter did not provide the identities and concentrations of these additives in the blended distillate fuels.

Because the distillate fuels are manufactured to meet performance specifications, their chemical compositions vary as do the component refinery streams, which are derived from different crude oils. Therefore, descriptions of the distillate fuels and gas oils category members are based on product history, physical properties (e.g., boiling point and viscosity) and product use specifications as well as the additives used in some of the members.

The distillate fuels and refinery streams covered under the category are listed in Table 1 and include the CAS number and name plus a short description if available, carbon number range, boiling point range ($^{\circ}F$) and/or viscosity (Saybolt universal seconds [SUS]).

CAS Numbers, CAS Names, and Descriptions for the Members of the Gas Oils Category

CAS Number	CAS Name	General Description, Carbon Number Range, Boiling Point Range and/or Viscosity (SUS)
<i>Distillate Fuels</i>		
68334-30-5	Diesel oil	C_9 - C_{20} , 163-357 $^{\circ}C$

68476-30-2	(Fuel oil no. 1-D) Fuel oil no. 2	C ₂₀ -C ₅₀ , 32.6-37.9 SUS at 37.7 °C
68476-31-3	Fuel oil no. 4	45-125 SUS at 37.7 °C
68476-34-6	Diesel fuel no. 2 (Fuel oil no. 2-D)	32.6-40.1 SUS at 37.7 °C

Refinery Streams

64741-43-1	Straight-run gas oils (petroleum)	C ₁₁ -C ₂₅ , 205-400 °C
64741-44-2	Straight-run middle distillates (petroleum)	C ₁₁ -C ₂₀ , 205-345 °C
64741-49-7	Vacuum tower condensates (petroleum)	Lowest boiling stream in vacuum distillation of residuum from atmospheric distillation of crude oil, C ₁₁ -C ₂₅ , 205-400 °C
64741-58-5	Light vacuum gas oils (petroleum)	Vacuum distillate obtained from residuum from atmospheric distillation, C ₁₃ -C ₃₀ , 230-450 °C
64741-59-9	Light catalytic cracked distillates (petroleum)	Effluent from catalytic cracking process, C ₉ -C ₂₅ , 150-400 °C
64741-60-2	Intermediate catalytic cracked distillate (petroleum)	Effluent from catalytic cracking process, C ₁₁ -C ₃₀ , 205-450 °C
64741-77-1	Light hydrocracked distillate (petroleum)	Effluent from hydrocracking process predominantly containing saturated hydrocarbons, C ₁₀ -C ₁₈ , 160-320 °C
64741-82-8	Light thermal cracked distillates (petroleum)	Effluent from thermal cracking process, C ₁₀ -C ₁₈ , 160-370 °C
64741-86-2	Sweetened middle distillates (petroleum)	Conversion of mercaptans and removal of acidic compounds, C ₉ -C ₂₀ , 150-345 °C
64741-90-8	Solvent refined gas oils (petroleum)	Predominantly aliphatic hydrocarbons, C ₁₁ -C ₂₅ , 205-400 °C
64741-91-9	Solvent refined middle distillates (petroleum)	Predominantly aliphatic hydrocarbons, C ₉ -C ₂₀ , 150-345 °C
64742-29-6	Chemically neutralized gas oils (petroleum)	Removal of acidic compounds, C ₁₃ -C ₂₅ , 230-400 °C
64742-30-9	Chemically neutralized middle distillates (petroleum)	Removal of acidic compounds, C ₁₁ -C ₂₀ , 205-345 °C
64742-38-7	Clay-treated distillates (petroleum)	Removal of trace amounts of polar compounds, C ₉ -C ₂₀ , 150-345 °C
64742-46-7	Hydrotreated middle distillates (petroleum)	Catalytic hydrogenation of petroleum fraction, C ₁₁ -C ₂₅ , 205-400 °C

CAS Numbers, CAS Names, and Descriptions for the Members of the Gas Oils Category (Cont.)

CAS Number	CAS Name	General Description, Carbon Number Range, Boiling Point Range and/or Viscosity (SUS)
64742-79-6	Hydrodesulfurized gas oils (petroleum)	Conversion of organosulfur to hydrogen sulfide through treatment with hydrogen, C ₁₃ -C ₂₅ , 230-400 °C
64742-80-9	Hydrosulfurized middle distillates (petroleum)	Conversion of organosulfur to hydrogen sulfide through treatment with hydrogen, C ₁₁ -C ₂₅ , 205-400 °C
64742-87-6	Hydrodesulfurized light vacuum gas oils (petroleum)	Effluent stream from catalytic hydrodesulfurization process, C ₁₃ -C ₃₀ , 230-450 °C
68333-25-5	Hydrodesulfurized light catalytic cracked distillates (petroleum)	Treatment of catalytically cracked distillate to convert organosulfur to hydrogen sulfide, also contains large proportion of bicyclic aromatic hydrocarbons, C ₉ -C ₂₅ , 150-400 °F
68333-88-0	Aromatic hydrocarbons, C ₉₋₁₇	C ₉₋₁₇
68477-31-6	Catalytic, reformer fractionator residue, low-boiling distillate (petroleum)	Distillate obtained from catalytic reformer fractionator residue, <288 °C
68814-87-9	Full-range straight-run middle distillates (petroleum)	C ₉ -C ₂₅ , 150-400 °C
68915-96-8	Straight-run, B. 557-880 degrees F., distillates (petroleum)	288-471 °C
68915-97-9	Straight-run, high-boiling, gas oils (petroleum)	282-349 °C

Category Justification

The submitter supports the grouping of the category members primarily by their similar process histories and physicochemical properties. The submitter also notes that the category members are primarily composed of saturated and aromatic hydrocarbons and that the ratio of these components varies continuously across the category members (see above in the category definition). The submitter then uses these characteristics to conclude that the physicochemical, environmental, and toxicological properties of the members will show a pattern that is associated with the aromatic to aliphatic ratio and will be bounded by members at either compositional extreme (i.e., a predominantly saturated and a predominantly aromatic stream will represent the range of physicochemical, environmental, and toxicological properties). Thus, the submitter concludes that the toxicities ("biological activity") of the members can be estimated from the results of tests performed on "representative gas oil streams 'enriched' in either saturated or aromatic hydrocarbons" and "data on the distillate fuels." The submitter also notes that a key element to consider when compositionally analyzing this category for some toxicity endpoints is the percentage of 3- to 7-ring PACs.

For the physicochemical endpoints, the properties of the distillate fuels and gas oils are defined by a range of values reflecting the differences in the class (i.e., paraffins, olefins, naphthenes, and aromatic hydrocarbons) and carbon number of the individual hydrocarbons in these complex mixtures. The submitter, however, did not describe how differences in the ratio of aromatic and aliphatic hydrocarbons will affect the physicochemical properties (a basic tenet of the test plan) and no information was presented from which to determine how any of the fuel oil additives affect the properties.

The fate of the distillate fuels and gas oils depends on the class and molecular weight and, from the information presented in the test plan, will generally follow a pattern across the category members for all but the biodegradation endpoint. EPA agrees that: a) overall, members with relatively lower molecular weights and higher volatilities will partition to the air more than the higher molecular weight components; b) once in air, they will be removed by reaction with hydroxyl radicals independent of their class; c) less volatile members tend to partition to soils and sediments, also independent of class; and d) the hydrocarbons in all of the distillate fuels and gas oils are stable in water. The rate and extent of biodegradation of the distillate fuels and gas oils will likely depend on the carbon number and structure of the individual hydrocarbons in these substances, but little information was presented in the test plan and no pattern could be identified. In general, the information available supports the grouping of the category members, but no discussion relating the class to environmental behavior was presented in the test plan.

The information provided in the test plan for health effects endpoints does not appear to support the hypothesis that toxicity will increase with increasing aromatic content for either the gas oils or the fuel oils for all HPV Challenge endpoints; however, there is some indication that substances enriched in aromatic hydrocarbons tend to produce more severe irritation in dermal and eye testing. No information was provided by the submitter to test the hypothesis that PACs contribute to the toxicity of the category members. Acute oral and dermal LD₅₀ values and LC₅₀ values were similar for gas oil streams containing either high or low aromatic content. Also, similar parameters were generally affected by gas oil streams of high or low aromatic content in dermal repeated-dose studies. The same was true for dermal developmental toxicity studies. (All longer-term toxicity studies for HPV program endpoints were by the dermal route except for a single inhalation developmental toxicity study that did not attain a maternally toxic concentration.) For example, the target organs were similar in 13-week dermal studies on a predominantly aromatic and a predominantly saturated gas oil (results from the predominantly saturated substance indicated that it was more toxic). Mixed results were obtained for genotoxic endpoints so that no clear pattern was seen based on aromatic content of the test substances. Therefore, while no pattern is apparent linking toxicity to the aromatic content of the category members, the similarity of some toxicities (e.g., similar target organs) suggests that the grouping of the members into the same category is supported. Nonetheless, if possible, the submitter needs to more clearly describe the patterns present in the data and discuss the influence of PACs (especially 3- to 7-ring PACs) and other components on toxicity.

The submitter did not provide sufficient information in the test plan to determine if a pattern is present for aquatic toxicity. Therefore, no conclusions can be drawn on how well available information supports the grouping of the category members.

Test Plan

General Comments

Publicly available data have been submitted to EPA for several of the CAS Nos. in this category (see <http://www.syrres.com/esc/tscats.htm>). The submitter should search these data (which include data from companies other than those listed as authors of the studies summarized in the robust summaries) to determine whether any studies can fulfill the missing endpoints. The majority of the data available are for the human health endpoints, but a few studies are available for other endpoints as well.

Physicochemical Properties (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The information provided by the submitter for photodegradation and stability in water are adequate for the purposes of the HPV Challenge Program.

Biodegradation. For biodegradation, EPA conditionally agrees with the choice of the two gas oil streams to be tested - one containing predominantly saturated hydrocarbons while the other contains predominantly aromatic hydrocarbons. These gas oil streams should first be characterized to identify their main components (e.g., the predominant chain lengths in the saturated stream) and their approximate molecular weights. The saturated stream must consist of predominantly noncyclic or cyclic hydrocarbons, but not both, since biodegradability may be different for the two types. When performing the biodegradation tests, the submitter needs to follow OECD TG 301 (tests for ready biodegradation).

Fugacity. The sponsor estimated the fugacity of these chemicals using a Level I EQC model. Although EPA had previously recommended the use of EQC Level I, this model is somewhat limited. EPA now recommends the use of the EQC level III model, which provides a more rigorous level of analysis. EPA believes that values based on a level III fugacity model are more realistic and useful for estimating a chemical's fate in the environment.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

General Comments. The substances included in this category need to be characterized with respect to the ranges of several components. First, occurrence of the 3- to 7-ring PACs should be characterized. Test data on substances that contain a range of levels of 3- to 7-ring PACs are needed for each SIDS endpoint.

Also, the percentage ranges of substances containing various heteroatom-containing compounds (containing N, O, S, and metals) also need to be specified for the category members and the potential toxicity of these substances needs to be addressed. If there are substantial amounts of these substances in the category members, additional test data may be necessary to adequately characterize the range of toxicity of these substances.

The test plan does present the olefin content of the gas oils. Substances proposed for testing should include a range of olefin levels.

General Comments, Distillate Fuels. The additive content is not characterized in the test plan or in the robust summary document for any of the distillate fuels. The additive content needs to be characterized for these fuels. If any additives are toxic, data on substances with a range of toxic additives need to be provided for each SIDS endpoint. Alternatively, data supporting the conclusion that the additives included in the distillate fuels are not expected to substantially affect toxicity need to be presented.

Acute Toxicity. It appears that adequate data may be available to satisfy this endpoint for all three sub-categories of gas oils. However, only toxicity values without associated robust summaries were provided for acute toxicity studies on the predominantly saturated gas oils. Therefore, a robust summary needs to be provided for a predominantly saturated gas oil that is one of the most acutely toxic.

Also, skin and eye irritation and skin sensitization data were described in the acute toxicity section of the test plan. These data need to be discussed in a separate section.

Repeated-Dose Toxicity. If the submitters can provide adequate discussion and resolution of the issues previously noted in the General Comments, then the data appear adequate to satisfy the repeated-dose toxicity endpoint of the distillate fuels and the predominantly saturated gas oils. However, additional data or testing on a predominantly aromatic gas oil is needed for the following reasons:

1. One robust summary (given a reliability code of 1) was for a study that used a 3-day/week dosing schedule for four weeks.
2. A second robust summary reported only limited results (skin irritation, growth rate, and mortality).
3. A third robust summary was assigned a reliability of 4.
4. The carcinogenicity data are not adequate based on the limited number of tissues microscopically examined and lack of clinical pathology examinations.

Because a reproductive/developmental screening study (OECD TG 421) is already being planned for a member of this subcategory, it may be appropriate to expand the study to include a repeated-dose component (OECD TG 422).

Genetic Toxicity. Data supplied for the chromosomal aberrations endpoint for the predominantly aromatic gas oils are adequate. Although adequate data may exist to satisfy the genotoxicity endpoints for the other subcategories, additional details need to be provided in the robust summaries so that the study adequacy can be independently assessed. Also, although carcinogenicity data can be used as supporting data as noted by the submitter, the data should not be used in place of adequate genotoxicity tests.

The test plan reported a range of mutagenicity indices for predominantly aromatic and predominantly saturated gas oil streams (p. 15). Mutagenicity indices, however, need to be associated with PAC levels (particularly 3- to 7-ring PAC levels if relevant data are available).

Reproductive and Developmental Toxicity. EPA agrees that additional testing is needed for the reproductive toxicity endpoint for the predominantly aromatic gas oils because the data provided only limited histopathology of reproductive organs. Owing to deficiencies in the repeated-dose endpoint for this subcategory, EPA recommends conducting a test according to OECD TG 422 as noted above.

EPA also agrees with additional testing for the distillate fuels, because only 28-day repeated-dose studies are available that evaluated reproductive toxicity. EPA understands that the submitter will conduct a test according to OECD TG 421 unless more extensive testing is done in coordination with a testing proposal by oil companies in the European Union. EPA encourages the submitter to inform EPA of any necessary information on the efforts to coordinate with their European counterparts.

Finally, EPA requests that the submitter provide the full study report of the 90-day repeated dose study (Mobil, 1991) on predominantly saturated gas oils. EPA reserves judgment on testing these oils pending an independent evaluation of the nature of the reproductive effects in this study.

As noted by the submitter, specific analytical data will be made available when the samples used in the proposed testing are obtained. This information should be as specific as possible, including the amount of 3- to 7-ring PACs, if possible. The test plan should also specify whether the samples can be associated with a particular CAS No. from the list of 28 substances.

The submitter needs to present robust summaries for the reproductive toxicity endpoint using the data from the repeated-dose toxicity studies and any new tests performed in a separate reproductive toxicity section in the Dossier.

Ecological Effects (fish, invertebrates, and algae)

No chronic aquatic toxicity data were included in the test plan or robust summary document for gas oils or for distillate fuels. Because the Log K_{ow} values of components of the gas oils range from approximately 3.9 to >6, there is a need for chronic aquatic toxicity data. EPA recommends that the submitter conduct chronic testing according to OECD TG 211 (on invertebrates). Such testing should be considered for all

subcategories. All testing should be conducted at or below the water solubility limit using mean measured concentrations.

As noted earlier, the submitter needs to characterize the percentages of heteroatom-containing compounds (N,O,S, and metals) in the gas oils. If there are significant amounts of these substances, the submitter should consider testing substances that have high-end percentages of these components.

General Comments, Distillate Fuels. No aquatic toxicity testing is planned for the distillate fuels. However, the performance additives in blended distillate fuels could affect their toxicity. Therefore, the test plan needs to characterize the possible range of additives contained in the test substances that have existing data so that it can be determined if the aquatic toxicity SIDS endpoints are adequately characterized with respect to these additives. Alternatively, the submitter could provide data supporting the conclusion that the additives in the distillate fuels are not expected to substantially affect toxicity to aquatic organisms.

The test plan needs to characterize and define the substances planned for testing, including the components in the substances as well as reasons for choosing those substances so that the choice can be independently evaluated.

The aquatic toxicity data were not adequately described in the test plan (p. 22) because there was no association between the reported toxicity values and the substances tested. A summary table would be a useful addition to the test plan.

Specific Comments on the Robust Summaries

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Fugacity. The submitter also needs to incorporate in the robust summary the values of the inputs used in the Fugacity Level III model.

Health Effects

Acute Toxicity, Predominantly Aromatic Gas Oils. Missing details in the submitted robust summaries included statistical methods and whether standard guidelines were used. Additional LD₅₀ values were also presented that did not have associated robust summaries. Although a reliability code of 1 was assigned to these data, sufficient detail was not reported. Therefore, an independent evaluation of data adequacy could not be performed.

Acute Toxicity, Predominantly Saturated Gas Oils. A robust summary for a GLP-compliant acute inhalation toxicity study in rats did not report the statistical methods used. Additional values (acute oral and dermal LD₅₀ values and acute inhalation LC₅₀ values) were also reported for several predominantly saturated gas oils. However, no information on the study methods or results were reported. Although a reliability code of 1 was assigned, insufficient detail was reported to allow an independent evaluation of data adequacy.

Acute Toxicity, Distillate Fuels. Sufficient detail was generally included in the robust summaries submitted for oral and dermal tests to allow for an independent evaluation of study adequacy. However, LD₅₀ values were also reported that did not have associated robust summaries. Although a reliability code of 1 was assigned to these studies, insufficient detail was reported to permit an independent evaluation of data adequacy. The conclusion presented in the robust summary on the dermal study indicating that "exposure to the test material did not cause any compound related changes" is not accurate because there were potential effects on the skin, liver, and kidneys. Therefore, this statement needs to be deleted.

Repeated-Dose Toxicity, Predominantly Aromatic Gas Oils. Robust summaries were submitted for a 4-week dermal study in rabbits and a 13-week dermal study in rats. The 4-week study was limited by application of the test material for only 3 days/week, and the 13-week study was limited by the small number of tissues microscopically examined and by the uncertainty of the clinical pathology tests performed. Also, results from other 4-week repeated-dose dermal tests in rabbits included only the dose, and effects on skin irritation, growth, survival. Therefore, these data are not adequate to satisfy the repeated-dose toxicity endpoint.

Repeated-Dose Toxicity, Predominantly Saturated Gas Oils. The robust summaries for a 4-week and a 13-week dermal study in rats are adequate, although the clinical pathology parameters were somewhat limited and use of standard guidelines was not indicated.

Genetic Toxicity, Predominantly Aromatic Gas Oils. A robust summary was submitted for an *in vitro* mutagenicity study in *Salmonella typhimurium* that tested cyclohexane/DMSO soluble extracts of three predominantly aromatic gas oils. Only strain TA98 was tested. Data missing from the robust summary included criteria for positive response or valid assay, incubation conditions (e.g., time, temperature), and number of replicate plates used. Also, results were not compared with a concurrent control group. Instead, a mutagenicity index (MI) was calculated, which represented the slope of the dose response curve.

A robust summary was also submitted for an *in vitro* mouse lymphoma forward mutation assay. Details missing from the robust summary included criteria for both a positive response and validity of the assay, incubation conditions (e.g., temperature), and number of replicates used.

Also, a table that summarized the results of mouse lymphoma assays for three predominantly aromatic gas oils was included; however, virtually no data on the methods or results were reported.

Results of testing two predominantly aromatic gas oils in *in vivo* cytogenetics tests were summarized in a table, and very brief robust summaries were provided for *in vivo* SCE assays; however, virtually no data on the study methods or results were reported in these summaries.

Genetic Toxicity, Predominantly Saturated Gas Oils. A robust summary was submitted for an *in vitro* mutagenicity study in *Salmonella typhimurium* that tested cyclohexane/DMSO soluble extracts of 11 predominantly saturated gas oils. Only strain TA98 was tested. Details missing from the robust summary included criteria for positive response or valid assay, incubation conditions (e.g., time, temperature), and number of replicates used. Also, results were not compared with a concurrent control group. Instead, a mutagenicity index (MI) was calculated, which represented the slope of the dose response curve.

Results from *in vitro* mouse lymphoma and sister chromatid exchange assays were briefly summarized for several predominantly saturated gas oils. However, virtually no details on the methods or results were reported.

Also, only brief robust summaries were provided for *in vivo* chromosomal aberrations for several saturated compounds and for a sister chromatid exchange assay. None of these summaries provided data on the study methods or results.

Genetic Toxicity, Distillate Fuels. A robust summary was submitted for an *in vitro* mutagenicity study in *Salmonella typhimurium* that tested cyclohexane/DMSO soluble extracts of three distillate fuel samples. A reliability code was not assigned to the data. Only strain TA98 was used. Data missing from the robust summary included criteria for positive response or valid assay, incubation conditions (e.g., time, temperature), and number of replicate plates used. Also, results were not compared with a concurrent control group. Instead, a mutagenicity index (MI) was calculated, which represented the slope of the dose response curve. Results from a study that used a more comprehensive set of *S. typhimurium* strains were

also presented in the robust summary; however, almost no details regarding the methods or results were reported. Additional details need to be provided before the data can be considered adequate.

A robust summary was also submitted for a pre-GLP *in vitro* mutagenicity study in cultured mouse lymphoma cells. Use of standard guidelines was not specified. The number of plates used/trial and incubation conditions were not specified and a reliability code was not assigned to the data. Also, it is not clear why the test substance was considered to be negative because it appeared to meet the criteria for a positive response. Although the data appear adequate, some discussion of these issues needs to be included in the summary. Results from testing another distillate fuel were summarized in the robust summary. However, virtually no details on the study methods or results were presented.

Robust summaries were submitted for a pre-GLP *in vivo* chromosome aberrations study in rats and an *in vivo* dominant/lethal mutation study in mice. Use of standard guidelines was not indicated. The summaries did not provide criteria for a positive response. The dominant/lethal mutation assay does not appear to be adequate unless the submitter can justify limiting the highest concentration tested to 400 ppm in the absence of any toxic responses.

Developmental Toxicity, Predominantly Saturated Gas Oils. Robust summaries for two GLP-compliant developmental toxicity screening studies in rats are not adequate due to the limited number of fetal evaluations.

Developmental Toxicity, Distillate Fuels. A robust summary was submitted for a pre-GLP inhalation developmental toxicity study in rats but the test substance was not tested up to a maternally toxic dose. It would be helpful if there were a justification for using a concentration of 400 ppm as the highest exposure level.

Ecological Effects

General. The summaries need to report water hardness where it is not supplied.

Invertebrates. Results from the analytical monitoring analyses were generally not reported. Also, the pH was exceptionally high (up to approximately 9.9) in many of the studies. The submitters noted that the organisms were cultured in the water with high pH and low mortality occurred in controls. Therefore, high pH may not have affected the results of the study. Also, the LC₅₀ values from these studies were generally comparable with results from studies that used pH conditions that were closer to neutral.

Algae. Results from the analytical monitoring analyses were generally not reported. Also, the temperature was outside the OECD recommended range in several of the studies; however, the magnitude of these changes were minor and probably did not substantially affect the study results.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.